Tab 23

OBESITY

Official Journal of the North American Association for the Study of Obesity
St. Luke's-Roosevelt Hospital Center
1090 Amsterdam Avenue, Suite 14K, New York, NY 10025

January 18, 2000

Douglas S. Kalman , MS, RD
Director, Clinical Research
Department of Medical Nutriiton
Peak Wellness, Inc.
50 Holly Hill Lane
Greenwich, CT 06830

Dear Mr. Kalman:

I regret to inform you that after careful review your manuscript (MS#B-99-117) entitled "**A Double-Blind, Placebo Controlled Clinical Trial Evaluating the Effects of An Over-the-Counter Weight Loss Aid in Healthy Overweight Adults**" has not been found acceptable for publication in *Obesity Research*.

Enclosed are the reviewers' comments to author(s), which we hope you will find helpful.

We want to thank you for giving us the opportunity to review your manuscript. We look forward to receiving other work from you in the future.

Sincerely,

F. Xavier Pi-Sunyer, M.D.
Editor-in-Chief

FXP/hrr
Enclosure

F. Xavier Pi-Sunyer, M.D., Editor-in-Chief • Helene Rosenhouse-Romeo, R.D., Managing Editor
Tel. (212) 523-2049 • Fax: (212) 523-2093 • E-mail: helener@mindspring.com

USI.5

OBESITY

Official Journal of the North American Association for the Study of Obesity
St. Luke's-Roosevelt Hospital Center
1090 Amsterdam Avenue, Suite 14K, New York, NY 10025

January 24, 2000

Nicholas Mezitis, MD
Obesity Research Unit
St. Luke's/Roosevelt
1111 Amsterdam Avenue
New York, NY 10025

Dear Dr. Mezitis:

Thank you for your expertise in reviewing the manuscript entitled "A Double-Blind, Placebo Controlled Clinical Trial Evaluating the Effects of An Over-the-Counter Weight Loss Aid in Healthy Overweight Adults" (B-99-117) for *Obesity Research*. I very much appreciate the time and effort that went into your review.

Based on reviewer comments, I have informed the author(s) that the manuscript has not been accepted for publication in the journal. You may now destroy your copy of the manuscript.

Once again, thank you for your invaluable participation in the peer-review process.

Sincerely,

F. Xavier Pi-Sunyer, M.D.
Editor-in-Chief

FXP/hrr
Enclosures

Obesity Research
1090 Amsterdam Avenue, Suite 14.

New York, NY 10025
Tel.: (212) 523-2049 Fax (212) 523-2098

Reviewer's Comments to the Editor

Manuscript Number: B-99-117
Reviewer's Name: Nicholas Mezitis, MD
Please Return By: January 06, 2000

"A Double-Blind, Placebo-Controlled Clinical Trial Evaluating the Effects of An Over-the-Counter Weight [illegible] Adults"

Recommendation	Publication Timing	Quality	Value	Yes	No	Uncertain
__Accept as is	✓ Routine	__Superior	Material Original?	__	✓	__
__Accept with minor revision	__ASAP	__Good	Data Valid?	__	__	✓
✓ Revise and reconsider		✓ Fair	Conclusions Reasonable?	__	__	__
(If you advise revision, are you willing to review revised version?) ✓ yes __no		__Poor	Info. Important?	✓	__	__
__Reject			Writing Clear?	__	✓	__
			General Medical Interest?	✓	__	__
			Tables/Fig. Appropriate? (If not explain)	✓	__	__
			Editorial Needed? If yes, I volunteer to write such,	✓	__	__
				__	__	
			or I suggest			

General Comments for Editor:

See comments to author.

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Obesity Research
1090 Amsterdam Avenue, Suite 14K
New York, NY 10025
Tel.: (212) 523-2049 Fax (212) 523-2098

Reviewer's Comments to the Author(s)

Manuscript Number: MS-B-99-117

"A Double-Blind, Placebo-Controlled Clinical Trial Evaluating the Effects of An Over-the-Counter Weight Loss Aid in Healthy Overweight Adults"

Reviewer's comments to the Author(s):

The study compares the effects of a proprietary weight loss compound, Xenadrine, on body weight and body composition in 12 healthy subjects, as compared to 13 subjects who received placebo. All subjects were instructed in an 1800 kcal/d NCEP Step I diet and they participated in a supervised exercise program three days/wk. In addition to the primary criteria of efficacy, serum chemistries, ECG and mood state profiling was undertaken at baseline, week 4 and week 8 of the study. Significant reductions in body weight and percent body fat are reported in the group which received verum, as compared to the placebo group.

My reservations include:

1. The exercise prescription (duration, activities) should be specified.
2. The mean reduction in weight achieved in the two study groups as reported in the text (Group 1 3.14 kg; Group 2 2.05 kg) should correspond to that calculated from Table I (Group 1 7.33 kg; Group 2 2.92 kg).
3. The percent weight change in the placebo group is 3.7% not 3.8%.
4. In the ECG analyses, QT intervals should be corrected for the R-R and the results should be included in the report.
5. Using a reference method would have enhanced body composition analysis.
6. Questions relating to the diet prescription are raised by the 3.5 kg loss of lean tissue in the placebo group over 8 weeks. This issue should be specifically addressed in the discussion
7. Were the effects of Xenadrine on sleep patterns evaluated?
8. Were subjects specifically questioned about the occurrence of palpitations, headaches, flushing?
9. What reasons were provided for dropout by the 5 subjects who were not included in the final analysis?
10. A reference should be provided for the Profile of Mood State test utilized in the study.
11. Is an 8 week trial sufficient time to address issues of efficacy in general and safety in particular for a weight-reducing agent?
12. The numerous errors in spelling, grammar and syntax scattered throughout the text should be corrected e.g. sympaticomimetic vs. sympathomimetic (p. 4), posit vs. postulate (p. 8), effect vs. affect (p.3), thereby vs. and therefore (p.4).

OBESITY

Official Journal of the North American Association for the Study of Obesity
St. Luke's-Roosevelt Hospital Center
1090 Amsterdam Avenue, Suite 14E, New York, NY 10025

January 24, 2000

Robert Kushner, MD
240 East Ontario, Suite 400
Chicago, IL 60611

Dear Dr. Kushner:

Thank you for your expertise in reviewing the manuscript entitled "A Double-Blind, Placebo Controlled Clinical Trial Evaluating the Effects of An Over-the-Counter Weight Loss Aid in Healthy Overweight Adults" (B-99-117) for *Obesity Research*. I very much appreciate the time and effort that went into your review.

Based on reviewer comments, I have informed the author(s) that the manuscript has not been accepted for publication in the journal. You may now destroy your copy of the manuscript.

Once again, thank you for your invaluable participation in the peer review process.

Sincerely,

F. Xavier Pi-Sunyer, M.D.
Editor-in-Chief

FXP/hrr
Enclosures

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Reviewer's Comments to the Editor

Manuscript Number: B-99-117
Reviewer's Name: Robert Kushner, MD
Please Return By: January 06, 2000

"A Double-Blind, Placebo-Controlled Clinical Trial Evaluating the Effects of An Over-the-Counter Weight Loss Aid in Healthy Overweight Adults"

Recommendation	Publication Timing	Quality	Value	Yes	No	Uncertain
__Accept as is	__Routine	__Superior	Material Original?	X		
__Accept with minor revision	__ASAP	__Good	Data Valid?			X
		__Fair	Conclusions Reasonable?		X	
__Revise and reconsider						
(If you advise revision, are you willing to review revised version?) __yes __no		X Poor	Info. Important?			X
X Reject			Writing Clear?		X	
			General Medical Interest?	X		
			Tables/Fig. Appropriate? (If not explain)		X	
			Editorial Needed?			
			If yes, I volunteer to write such.			
			or I suggest			

General Comments for Editor:

Too much data and description of methods, materials and results are excluded to fully evaluate importance and validity of study. It appears to be a poorly conducted study with suspect conclusions.

023

451.10

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Reviewer's Comments to the Author(s)

Manuscript Number: MS-B-99-117

"A Double-Blind, Placebo-Controlled Clinical Trial Evaluating the Effects of An Over-the-Counter Weight Loss Aid in Healthy Overweight Adults"

Reviewer's comments to the Author(s):

Summary

Authors conducted a double-blind, placebo controlled trial to evaluate the short term (8 weeks) effect of an over-the-counter weight loss aid in healthy overweight (BMI > 25) adults. Two groups were randomized to receive either placebo or a proprietary product, Xenadrine™, containing ephedrine alkaloids 20 mg, synephrine 5 mg, caffeine 200 mg, and salicin 15 mg, twice per day. The authors concluded that subjects randomized to Xenadrine™ lost significantly more body weight and percent body fat without experiencing adverse effects, indicating that the product was safe.

Specific Comments

1. Abstract. Several methodological issues and results were mentioned in the abstract but not referred to again or shown in the manuscript. These include: instruction by a R.D. on a 1800 kcal diet, performance of a 3 day/wk cross training exercise program under the guidance of an exercise physiologist, and the lack of changes in serum chemistries and caloric intake. If this information was important enough to mention in the abstract, it needs to be addressed in the body of the manuscript.
2. Introduction. The 3rd paragraph on the third page through the end of the 4th paragraph on the fourth page should be shortened and moved to the discussion section.
3. Materials and methods.
   a. There is no mention of gender among the 30 subjects.
   b. Why was a BMI of > 25 chosen for enrollment? Standard pharmacological therapy is indicated for patients with a BMI of at least 30 or 27 with co-morbid conditions.

c. Measurement of small changes in body composition by skinfold anthropometry is insensitive and unreliable. Thus, change in body weight alone should be the primary endpoint.

d. Describe what is assessed in the Profile of Mood State testing.

e. How were adverse effects evaluated? Was a questionnaire used to prompt subjects regarding symptoms, and if so, how were they recorded (yes or no, 5 point scale, ect.)?

f. How was dietary instruction provided? Individually or group, what materials were used, was there reinforcement? Why was a 1800 kcal diet chosen for all subjects?

g. Describe cross training exercises. Where were they performed?

1. Results.
   a. What were the reasons for the 5 drop outs?
   b. State what the pill compliance rate was in the two groups.
   c. Results for weight loss difference between groups should statistically evaluate the change in weight (mean ± SD), not only absolute body weight before and after treatment. I suspect that this value will not be statistically significant.
   d. Data for change in body composition by skinfold anthropometry is suspect due to low sensitivity and reproducibility of the method.
   e. It is surprising that no change in heart rate was noted in the treatment group based on the product's ingredients. This data should be shown.
   f. A symptom list should be shown for the two groups to ensure that specific side effects were queried.
   g. It is stated on page 8 that, "... each subject in this study ate 22 kcal/kg, and there was no significant difference between the two groups in overall caloric intake." How was this conclusion arrived at?
   h. What was the compliance with the exercise program?
1. Tables 1 and 2. The baseline data in repeated in the two tables and is therefore redundent. A Table should be added to show a symptom list
2. A figure should be added to show mean and SD weight loss of the two groups at 4 and 8 weeks.

General Comments

1. The study length is exceptionally short. It should be extended to at least 6 months and preferably 1 year.
2. The conclusion that "a decrease in the metabolic rate was countered by a stimulation of lipolysis" is not justified. There was no measurement of basal metabolic rate (BMR) nor lipolysis performed in the study. Furthermore, the absence of any change in pulse rate or development of any other symptoms in the treatment group is not consistent with the product as a "thermogenic, sympathicomimetic stimulant."
3. Funding source for the study needs to be clearly stated. Was this study supported by Cytodyne Technologies?

651.12

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St. Luke's-Roosevelt Hospital Center
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Journal of
Bio-Behavioral
Biochemistry
Clinical
Eating Disorders
Epidemiology
Ethnicity
Clinical
Nutrition
Metabolism
Pediatrics
Physiology
Psychology
Surgery

Society for
Obesity

January 24, 2000

James W. Anderson, MD
University of Kentucky
Metabolic Research Group
2250 Leastown Road (111C)
Lexington, KY 40511-1093

Dear Dr. Anderson:

Thank you for your expertise in reviewing the manuscript entitled **"A Double-Blind, Placebo Controlled Clinical Trial Evaluating the Effects of An Over-the-Counter Weight Loss Aid in Healthy Overweight Adults"** (B-99-117) for *Obesity Research*. I very much appreciate the time and effort that went into your review.

Based on reviewer comments, I have informed the author(s) that the manuscript has not been accepted for publication in the journal. You may now destroy your copy of the manuscript.

Once again, thank you for your invaluable participation in the peer-review process.

Sincerely,

F. Xavier Pi-Sunyer, M.D.
Editor-in-Chief

FXP/hrr
Enclosures

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Reviewer's Comments to the Editor

Manuscript Number: B-99-117
Reviewer's Name: James W. Anderson, MD
Please Return By: December 27, 1999

"A Double-Blind, Placebo Controlled Clinical Trial Evaluating the Effects of An Over-the-Counter Weight Loss Aid in Healthy Overweight Adults"

Recommendation	Publication Timing	Quality	Value	Yes	No	Uncertain
__Accept as is	__Routine	__Superior	Material Original?	✓		
__Accept with minor revision	__ASAP	__Good	Data Valid?			✓
__Revise and reconsider		__Fair	Conclusions Reasonable?			✓
(If you advise revision, are you willing to review revised version?) __yes __no		✓Poor	Info. Important?			✓
✓Reject			Writing Clear?		✓	
			General Medical Interest?	✓		
			Tables/Fig. Appropriate? (If not explain)	✓		
			Editorial Needed? If yes, I volunteer to write such,		✓	
			or I suggest			

General Comments for Editor:

Comment & edits e-mailed

No comment to author

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III

Reviewer's Comments to the Author(s)

Manuscript Number: MS-B-99-117

"A Double-Blind, Placebo Controlled Clinical Trial Evaluating the Effects of An Over-the-Counter Weight Loss Aid in Healthy Overweight Adults"

Reviewer's comments to the Author(s):

This study has serious flaws. I can accept a small difference in weight loss between the two groups but the body composition changes are crude and of limited value. Too much data and description of methods, materials and results are excluded to fully evaluate the importance and validity of this study.

451.15